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Photorefractive keratectomy in high myopic defects with or without intraoperative mitomycin C: 1-year results

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PURPOSE. *To study the results of the prophylactic use of mitomycin C (MMC) to reduce haze formation and refractive regression after excimer laser photorefractive keratectomy (PRK) for high myopic defects (>5 diopters).*
METHODS. *Prospective, consecutive, observational study. A total of 124 eyes of 62 patients were divided into two groups of 31 patients, 62 eyes each (Groups A and B). Only Group A was treated with MMC 0.02%. The data of the two groups of eyes, related to the best-corrected visual acuity (BCVA), to the difference of refraction pre- and post-treatment, and to the corneal haze, were analyzed through combined permutation tests by using the NPC Test software.*
RESULTS. *BCVA of Group A, 1 year after treatment, was better than that of the control Group B (one-sided p value = 0.013): Group A – 3 eyes (4.8%) had a loss of a decimal fraction and no eyes > 1; Group B – 13 eyes (20.9%) had a loss of a decimal fraction and 1 eye (1.6%) of 2. There was a smaller difference between attempted and achieved SE correction in Group A with respect to Group B (one-sided p value = 0.068): Group A – 43 eyes (69.3%) within ± 0.50 D; Group B – 31 eyes (50%) within ± 0.50 D. there was a smaller incidence of corneal haze in the group for which MMC was used (one-sided p value = 0.005).*
CONCLUSIONS. *In this study, the application of MMC 0.02% solution immediately after PRK produced lower haze rates and had better predictability and improved efficacy 1 year after treatment. (Eur J Ophthalmol 2006; 16: 229-34)*

KEY WORDS. *Corneal haze, Corneal wound healing, Mitomycin C, Refractive surgery, Visual acuity*

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INTRODUCTION

Excimer laser photorefractive keratectomy (PRK) achieves good visual results in the treatment of myopia, hyperopia, and astigmatism, especially in patients with mild to moderate myopia.

Development of corneal opacity and refractive regression are the main obstacles, especially when higher corrections are attempted (1-3).

Although several therapeutic agents to reduce haze formation after PRK have been proposed and tested, their efficacy has not been proven.

Recently, several studies have proposed the intraoperative topical use of a 0.2 mg/mL diluted mitomycin (MMC) solution, applied after high myopic PRK correction, as potential modulator of the wound healing (4-11).

The purpose of our study is to evaluate the results of the refraction, visual acuity, and corneal haze 1 year after PRK correction in two groups of eyes with or without the intraoperative topical use of MMC 0.02%.

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METHODS

A total of 124 eyes of 62 patients (27 men and 35 women) were enrolled in our prospective, consecutive, observational study.

Inclusion criteria were age between 22 and 60 years, at least 1 year of refractive stability before surgery, and an attempted spherical equivalent (SE) correction greater than -5.0 diopters (D).

Exclusion criteria were previous ocular surgery, history of severe ocular trauma, ocular or systemic diseases potentially interfering with corneal healing (dry eye syndrome, anterior or posterior uveitis, collagenopathies, diabetes), corneal dystrophies or degeneration (including endothelial dystrophies), keratoconus and other ectatic diseases (detected by videokeratography), chronic or acute glaucoma, retinal diseases, or lens opacity and a calculated residual corneal thickness postablation inferior 400 microns (detected by ultrasound corneal pachymetry).

Sixty-two patients were divided into two groups of 31 patients each (11 men and 20 women, 62 eyes, in Group A and 13 men and 18 women, 62 eyes, in control Group B).

Randomization was performed using envelopes that contained the group assignment. Before each surgery, 1 envelope was opened to disclose the assignment. During follow-up examinations, none of the examiners was aware of the link group of the patients in the study.

Preoperative examination included manifest and cycloplegic refraction (1% cyclopentolate hydrochloride eye drops), slit-lamp microscopy of the anterior and posterior chamber, tonometry, corneal topography assessment (Eyetop-CSO, Firenze), and corneal pachymetry (Pachette, DGH).

Best-corrected visual acuity (BCVA) was tested at 5 m using the HTVO visual acuity test (M.A.V., SIFI, Catania, Italy) and expressed as decimal fraction.

Follow-up examinations involved the tests and assessments performed during the preoperative visit except for the cycloplegic refraction.

The corneal haze detected during the follow-up was evaluated by a masked investigator and graded according to a 0 to 4 scale: grade 0 = totally clear cornea, grade 1 = trace haze of minimal density seen only by indirect tangential illumination, grade 2 = mild haze, visible with direct local slit illumination, grade 3 = moderate haze that partially obscures iris details, and grade 4 = severe haze that completely obscures iris details (12).

Myopic correction was done using the Bausch & Lomb Technolas 217 C excimer laser.

All the ablations had an optical zone included between 5.4 and 6.0 mm with an additional 3.0 mm transition zone diameter.

The statistical analysis was based on combined permutation tests (13, 14).

First, marginal permutation tests were respectively performed for the right and the left eye subgroups in order to avoid intraindividual effects.

Subsequently, the marginal tests were nonparametrically combined by means of the combination procedure proposed in order to obtain global p values (i.e., combining the right and left eye tests) for the BCVA (p=0.013), for the difference in attempted and achieved SE correction (p=0.068), and corneal haze (p=0.005).

The study was conducted at a site that did not have an institutional review board or ethics committee, although the experimental nature of the treatment was explained to the patients, who provided informed consent.

Photorefractive keratectomy procedure

Every treatment was performed under topical anesthesia with a mechanical disepithelization through Amoils's brush.

Immediately after the laser treatment, the study group eyes (A) received a single topical application of mitomycin C 0.2 mg/mL diluted in balanced salt solution (BSS), mixed fresh every laser session. This was administered by placing a soaked 8.0 mm Merocel sponge over the ablated stroma. The sponge was kept in place for 2 minutes. The corneal surface and the entire conjunctival sac was then irrigated with BSS (20 cc) to remove the residual MMC. The control group eyes (B) did not receive this therapy.

All eyes received the same postoperative therapy. A bandage contact lens was applied at the end of the procedure and removed after re-epithelization. Antibiotic drops (netilmicin) were given four times daily until re-epithelization.

Once re-epithelization occurred, all eyes were treated with artificial tears (hyaluronic acid) and corticosteroid drops (fluorometholone sodium 1%) three times daily for the first month, then twice per day for 15 days. No additional steroids were used during the follow-up.

Daily controls were performed until corneal re-epithelization (not noticing differences of time, pain, or side effects among the two groups) then to 1, 3, 6, and 12

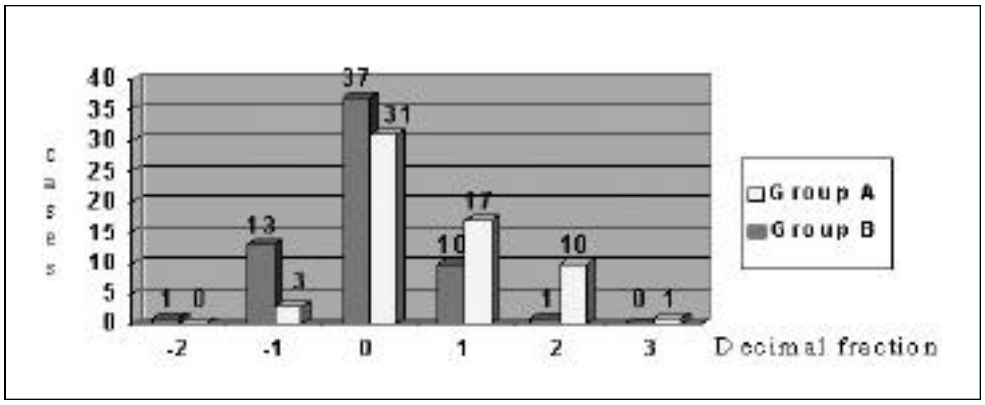

Fig. 1 - *Best-corrected visual acuity change from baseline to 12 months after photorefractive keratectomy.*

months; these examinations involved the tests and assessment performed during the preoperative visit except for the cycloplegic refraction.

RESULTS

In Group A, the mean patient age was 36.0 years (range 22 to 54 years), the mean myopia was 7.36 D ± 2.21 SD (range -3.25 to -14.00 D), the mean astigmatism was 0.88 D ± 0.89 SD (range 0 to -3.50 D). The BCVA average was 0.83 ± 0.14 SD; 19 eyes (30.6%) had a preoperative BCVA of 1.0 (equivalent to 20/20) or better and 51 (82.2%) of 0.8 (equivalent to 20/25) or better.

The mean attempted SE correction was -7.55 D ± 1.55 SD (range 5.25 to 11.00 D) and the mean attempted cylindric correction was -0.77 D ± 0.94 SD.

In Group B the mean patient age was 35.6 years (range 26 to 60 years), the mean myopia was 6.70 D ± 1.80 SD (range -3.00 to -12.50 D), the mean astigmatism was 0.89 D ± 0.84 SD (range 0 to 3.25 D). The BCVA average was 0.88 ± 0.11 SD; 20 eyes (32.2%) had a preoperative BCVA of 1.0 (20/20) or better and 53 (85.4%) of 0.8 (20/25) or better.

The mean attempted SE correction was -7.04 D ± 1.56 SD (range 5.25 to 11.00) and the mean attempted cylindric correction was -0.80 D ± 0.84 SD.

There were no differences between the two groups in age (two-sided p value > 0.05), in BCVA (two-sided p value > 0.05), or in attempted correction (two-sided p value > 0.05). The p values were obtained on the basis of permutation tests. Marginal permutation tests were individually performed for the right and the left eyes and they were nonparametrically combined to compute the p values in the case of the BCVA and of the attempted correction.

In our study we analyzed, 1 year after PRK, the BCVA, the attempted versus achieved spherical equivalent correction, and the corneal haze.

The BCVA results at 1 year are shown in Figure 1. In Group A only 3 eyes (4.8%) had a loss of a decimal fraction, 31 eyes (50%) any variation, 17 eyes (27.4%) a profit of a decimal fraction, 10 (16.1%) of 2, and 1 eye (1.6) of 3. The BCVA average was 0.9 ± 1.40 SD.

In Group B, in 37 eyes (59.6%) there was no difference of BCVA, in 13 eyes (20.9%) a loss of a decimal fraction, and in 1 eye (1.6%) of 2, while 10 eyes (10.6%) have shown an improvement of a fraction and in 1 eye (1.6%) of 2. The BCVA average was 0.88 ± 1.46 SD (Fig. 1).

The second analyzed aspect was the difference between attempted and achieved SE correction 1 year after the treatment.

In the study group (A) 24 eyes (38.7%) did not show any difference: 19 eyes (30.6%) were within ± 0.5 D of the intended correction, 13 eyes (20.9%) within ± 1 D, and 6 eyes (9.6%) within ± 1.5 D.

In the control group (B), 19 eyes (30.6%) did not show any difference, 22 eyes (35.4%) were within ± 0.50 D of the intended correction, 7 eyes (11.2%) within ± 1 D, 7 eyes (11.2%) ± 1.5 D, 3 eyes (4.8%) ± 2.0 D, 2 eyes (3.2%) ± 2.5 D, 1 eye (1.6%) ± 3 D, and 1 eye (1.6%) ± 4 D (Fig. 2).

The last examined aspect was the corneal haze. The eyes treated with MMC (A) showed in 92.5% (58 eyes) a haze 0 and in the remaining percentage (4 eyes) a haze 1, while in the other group (B) 75.8% of the cases (47 eyes) showed a haze 0, 12.9% (8 eyes) a haze 1, and 11.3% (7 eyes) a haze 2 (Fig. 3).

No eye treated with MMC showed toxic effects due to the drug.

As previously mentioned in Methods, the inference was carried out by means of combined permutation tests in

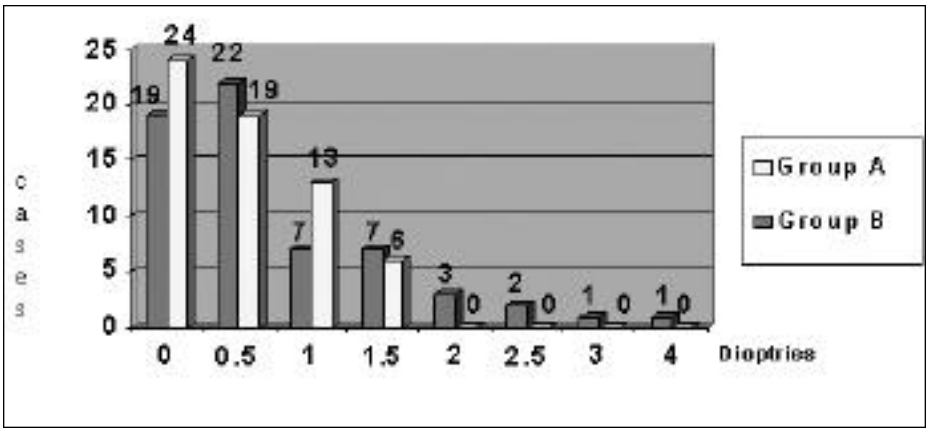

Fig. 2 - *The differences between attempted and achieved correction 12 months after photorefractive keratectomy.*

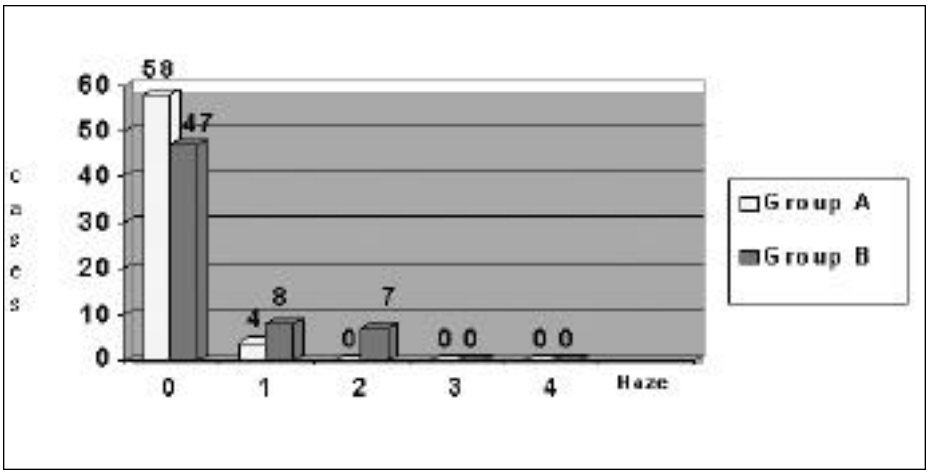

Fig. 3 - *Corneal haze, 1 year after photorefractive keratectomy.*

order to assess the null hypothesis of no-group effect for the three considered variables, i.e., the BCVA, the difference between the attempted and achieved correction, and the corneal haze. Standard statistical techniques were not appropriate in this setting, since a bias could be introduced by a lower intraindividual variation (the left-and-right-eye effect) if the eyes in each group were jointly considered. Hence, for overcoming this effect, we have adopted a recently introduced (but well-established) statistical technique, i.e., the combined permutation testing procedure proposed by Pesarin (13). By adopting this procedure, in the first stage the marginal permutation tests were respectively performed for the right and the left eye subgroups in order to avoid intraindividual effects. Subsequently, in the second stage the marginal tests were nonparametrically combined in order to obtain global p values. In this way the dependence structure of the marginal tests is captured by the combined permutation procedure. The data were analyzed on the basis of this method by using the software NPC Test 2.0 by Methodologica Srl, Treviso, Italy. On the basis of the previous procedure, the following inferential conclusions may be drawn:

The BCVA of the study group (MMC) seems to be significantly better than that of the control group (global one-sided p = 0.013)

The difference between attempted and achieved SE correction is likely to be smaller in Group A with respect to Group B (global one-sided p = 0.068)

The incidence of corneal haze seems to be significantly smaller in the MMC group (global one-sided p = 0.005)

DISCUSSION

MMC is an alkylating antibiotic agent derived from Streptomyces caespitosus that blocks DNA and RNA replication and protein synthesis. The compound is metabolized by liver enzymes to form an alkylating agent

that nonspecifically crosslinks with DNA in a cell-dependent manner (15). MMC inhibits mitosis and the proliferation of capillary and corneal endothelial cells, corneal epithelial cells, conjunctival cells, Tenon's capsule fibroblasts, and other fibroblasts (11, 16-19).

The first description of the use of MMC in ophthalmology appeared in 1963 in the study of Kunimoto and Mori, who employed it for its cytostatic effect on tissue in pterygium surgery.

Subsequently, numerous studies on animals and humans proposed the application of MMC after glaucoma surgery, pterygium excision, and in the treatment of conjunctival and corneal intraepithelial neoplasia and ocular pemphigoid (20-23).

The first application of MMC after refractive surgery with excimer laser was presented by Talamo et al, who showed on the rabbit in 1991 that a topical association of MMC and steroids reduced subepithelial scar more than single steroid (Talamo JH, Lee K, Puliafito CA, Steinert RF, ARVO Abstract 1247, 1991) (4). MMC reduces keratocytes in the anterior stroma after corneal refractive surgery, leading to a decrease in activated fibroblasts, production of extracellular matrix, and formation of corneal haze (11).

Other authors have confirmed this result in rabbit studies (5, 6).

Majmudar et al had good results with a unique application of MMC 0.02% at the end of refractive surgery in a group of eight human eyes with subepithelial fibrosis and reduction of VA secondary to RK and PRK and failed phototherapeutic treatments. The results were good on disappearance of the haze and on its refractive regression, with improvement of VA (7). This good result has been confirmed by other authors (8, 10).

In 2001, Azar and Jain warned against the possible toxicity of MMC, recommending the use of diskettes with central opening of 3 mm diameter soaked in MMC to apply at the end of the photoablation, to the dose of 0.05%, for 1 minute. This type of application would be supported by the fact that the activated keratocytes, important for the scarring, are those that depart from the periphery of the ablation zone and because it is preserved the central zone of the cornea by the possible toxicity of the MMC (9).

One case report describes a corneal scleral melt that occurred after a single intraoperative application of MMC 0.02% for 3 minutes to the sclera after pterygium surgery. Compared to our study, the longer exposure time and the different location of the MMC (scleral versus cornea) could explain the toxic effect.

The other cases of corneal toxicity with MMC use are all associated with prolonged topical use of MMC (24, 25).

The unique application at the end of surgery is less toxic, above all for the corneal epithelium, and improves the patient's compliance (26).

Therefore, from February 2001 to September 2002, we have been using MMC in selected cases of high myopic defects submitted to PRK according to the protocol of Majmudar et al (7) (only one application at the end of the photoablation for 2 minutes to the dose of 0.02% followed by abundant washing with BSS), in an attempt to reduce corneal haze and regression – the two greatest postoperative complications of PRK in the correction of high myopic defects.

MMC is able to favorably influence the formation of corneal haze in our patients.

Diminution of the activated keratocytes, shown by the rabbit studies (4-6), but also in human eyes with the confocal microscope (3), explain the reduction of keratocyte density in the anterior stroma, that is, together with the deposition of extracellular material, at the basis of the formation of the haze and the subepithelial fibrosis.

In our study, the refractive regression has been influenced favorably by the use of MMC, even if the follow-up is still insufficient to definitively judge the stability of the achieved result. Some studies have, in fact, shown that the regression can also be revealed after the 12th month from treatment (1, 2).

The possible toxicity of MMC reported by other publications (9, 24, 25, 27) has never been manifested in the eyes treated by us, maybe owing to the single application at the end of the intervention and the concentration (0.02%) and the exposure time (only 2 minutes), which seems to induce apoptosis and not necrosis (11).

In our study, we have tried to evaluate whether meaningful statistical differences were present 1 year after treatment relative to BCVA and predictability and degree of corneal haze between eyes submitted to PRK for high myopic defects (>5 D) with or without the intraoperative use of a mitomycin solution. Based on our study it is possible to affirm that the intraoperative application of MMC after PRK for myopic defects >5 D produces the best BCVA results, greater predictability, and smaller corneal haze, but the use of MMC is not justified in all eyes submitted to PRK, because a greater number of cases and a longer follow-up are necessary and because in the cor-

rection of mild to moderate myopic defects, the haze and the refractive regression are a very limited problem.

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